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Structural Characterisation of Cu Complexes of Chiral Ferrocenyl Diphosphine Ligands

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Abstract: Copper complex formation of JosiPhos-type ligands leads to extreme differences in solubility between the racemate and the enantiomers.

Key words: copper complex, chiral ferrocenyl ligand, amplification, solubility

Over the last few decades, many asymmetric catalytic transformations have been developed using chiral ligands in combination with transition metals.[1] The introduction of the bidentate chiral phosphine DIOP by Kagan marked the beginning of the era of bidentate phosphine ligands in asymmetric catalysis. Examples comprising P,P ligands are BINAP, DuPhos, DiPAMP, TRAP, JosiPhos, XyliPhos, TaniaPhos and WalPhos-type ligands.[2] These ligands have been used in many asymmetric transformations such as hydrogenation, alkene hydroboration, hydrophosphination, Heck reactions, conjugate additions and so on.[1b]

Recently, we reported a dramatic asymmetric amplification in the 1,2-addition of Grignard reagents to enones in *t*-BuOMe (Scheme 1), catalysed by a copper complex of the chiral ferrocenyl diphosphine ligand rev-JosiPhos.[3] It was made plausible that the strong asymmetric amplification is not specific to this particular reaction but is in fact due to significant differences in the solubility of the racemic and the enantiopure catalyst. Complexation of a transition metal with a number of chiral diphosphine ligands led to extreme differences in solubility between the enantiopure and the racemic complexes.[3c]

Here we report the structural characterisation of a number of copper complexes of racemic and enantiopure ferrocenyl diphosphine ligands in the solid state and in solution. We discuss their physicochemical properties and provide an explanation for the previously obtained amplification phenomenon.

The dramatic difference in solubility of the chiral copper complex of rev-JosiPhos found in our previous studies[3c] is the primary factor for the previously observed asymmetric amplification.

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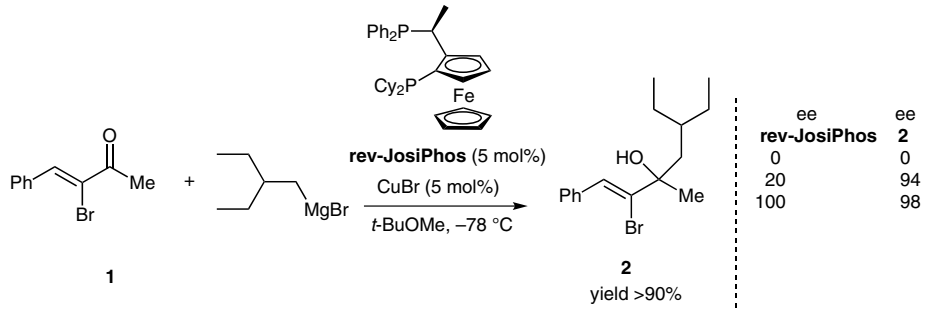
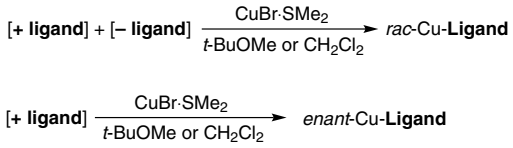
Syuzanna R. Harutyunyan is currently a tenured Associate Professor in Synthetic Organic Chemistry at the University of Groningen. Harutyunyan's group research activities include enantioselective synthesis, organometallic reactions, catalysis, autocatalysis, mechanistic studies. Part of this work has resulted in winning the prestigious Solvias Ligand Contest in 2011 and highly competitive NWO-Vidi award in 2012. Before joining the University of Groningen to occupy a tenure-track position, she carried out research in Armenia, Russia, Poland, Belgium, and in the Netherlands. She worked for two years as a senior scientist at Tibotec-JanssenPharmaceutica-J&J (Belgium). The research was focused on the development of new patent-free metathesis catalysts, for synthesis of an anti-hepatitis drug and the implementation of new procedures to scale up production. During her postdoctoral with Prof. Ben Feringa (Netherlands) her research led to the discovery of the first enantioselective catalytic methodologies using Grignard reagents, and revealed the mechanisms of these reactions and application of these methodologies in total synthesis of natural products. As a visiting scientist in the group of Prof. K. Grela (Poland) she worked on the synthesis and the application of metathesis catalysts. During her PhD research under supervision of Prof. Yu. N. Belokon (Russia) she developed new strategies for enantioselective synthesis of amino acids in phase-transfer-conditions. Syuzanna obtained her masters degree in pharmacology at Yerevan State University.

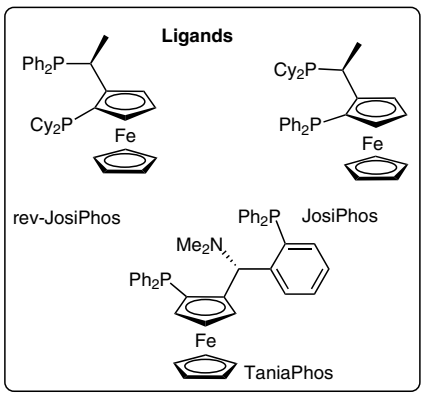
Therefore we chose copper complexes of rev-JosiPhos and the related ligands JosiPhos and TaniaPhos, all commonly used in asymmetric catalysis, for the studies reported here (Scheme 2).[4] Both the racemic and the enantiopure copper complexes were prepared in *t*-BuOMe or CH_2Cl_2 (0.015 M) by mixing the corresponding chiral racemic and enantiopure ligands with the corresponding amount of copper salt at room temperature for one hour. In both solvents a significant amount of precipitate formed in the case of the racemic complex of rev-JosiPhos, while the enantiopure complex was fully soluble. A racemic sample was obtained by simple filtration of the reaction mixture and the enantiopure complex was obtained by removal of the remaining solvent. In the case of JosiPhos and TaniaPhos both the racemic and the enantio-



Scheme 1 Asymmetric amplification in 1,2-addition of Grignard reagents to ketones

pure complexes were obtained by solvent removal either from *t*-BuOMe or CH_2Cl_2. To understand the structural differences between the racemic and the enantiopure complexes, we first studied the species formed in solution. The initial hypothesis was that dinuclear and mononuclear species can have different solubilities, and depending on whether the ligand is racemic or enantiopure, either of the two species is formed. To confirm this hypothesis we first studied solutions (in CH_2Cl_2 and *t*-BuOMe) and solid samples of both racemic and enantiopure complexes using high resolution ESI–MS and DART–MS[5] spectrometry. Unfortunately, molecular ions corresponding to dimeric and monomeric species were found for all samples, so this was inconclusive.





Scheme 2 Structures of chiral ferrocenyl diphosphine ligands used for the synthesis of racemic and enantiopure copper complexes

No significant differences were observed in the ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR spectra for the copper complexes of the racemic and enantiopure ligands.

To reveal the composition of the copper complexes in the solid phase, crystals of racemic and enantiopure copper complexes of all three ligands were grown and subjected to X-ray crystallography.[6,7]

The crystal structures of the Cu complexes of rev-JosiPhos show a dimeric structure for both the racemate[8,9] and the single enantiomer, albeit with a different symmetry (Figure 1, a and b).[6,7]

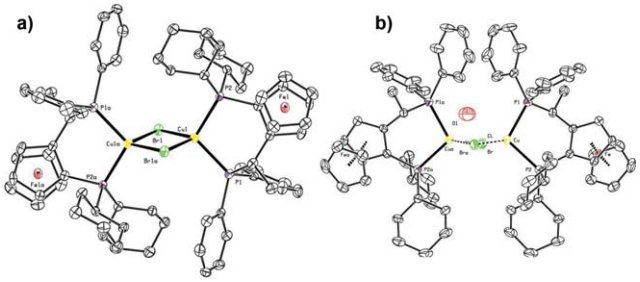


Figure 1 X-ray crystal structures[6,7] of the copper bromide complexes of rev-JosiPhos: (a) *rac*-CuBr-rev-JosiPhos; (b) *enant*-CuBr-rev-JosiPhos (the asymmetric unit consists of a dinuclear copper complex, with a molecule of water present in the cell).[6a]

In both cases the unit cell consists of one moiety of a dinuclear copper complex, bridged by two Br atoms. Analysis of the crystal structures of the racemate and single enantiomer of Cu/JosiPhos revealed monomeric structures (Figure 2a). Similarly the racemate and the single enantiomer[7] of Cu/TaniaPhos showed monomeric structures.

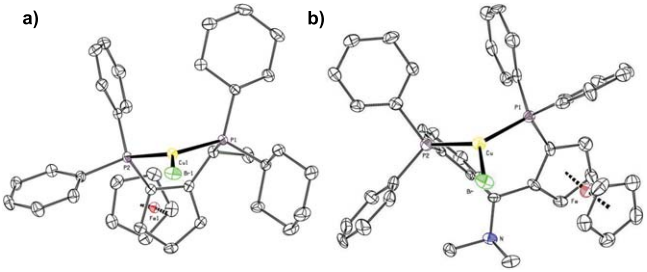


Figure 2 X-ray crystal structures[6,7] of the copper bromide complexes of JosiPhos and TaniaPhos: (a) *rac*-CuBr-JosiPhos; (b) *rac*-CuBr-TaniaPhos. For enantiopure structures of CuBr-JosiPhos and CuBr-TaniaPhos see ref. 4 and Supporting Information correspondingly.

When we compared the crystal structures of the racemates and the single enantiomers, we made the interesting observation that racemic Cu/rev-JosiPhos and Cu/JosiPhos have a higher density and a higher packing index than the single enantiomers (Table 1).[10]

Table 1 Crystal Packing Characteristics[6,7]

CuBr-Ligand	CCDC number	Space group	D_x [g/cm]	K.P.I.10
rac-CuBr-rev-JosiPhos	CCDC 908802	C2/c (no. 15)	1.545	69.8%
enant-CuBr-rev-JosiPhos	CCDC 610500[a]	$C222_1$ (no. 20)	1.475	67.0%
rac-CuBr-JosiPhos	CCDC 908803	P1 (no. 2)	1.540	69.7%
enant-CuBr-JosiPhos	CCDC 261573	$P2_1$ (no. 4)	1.529	69.3%
rac-CuBr-TaniaPhos	CCDC 908804[b]	$P2_1/c$ (no. 14)	1.539	68.0%
enant-CuBr-TaniaPhos	CCDC 909403	$P2_12_12_1$ (no. 19)	1.539	68.5%

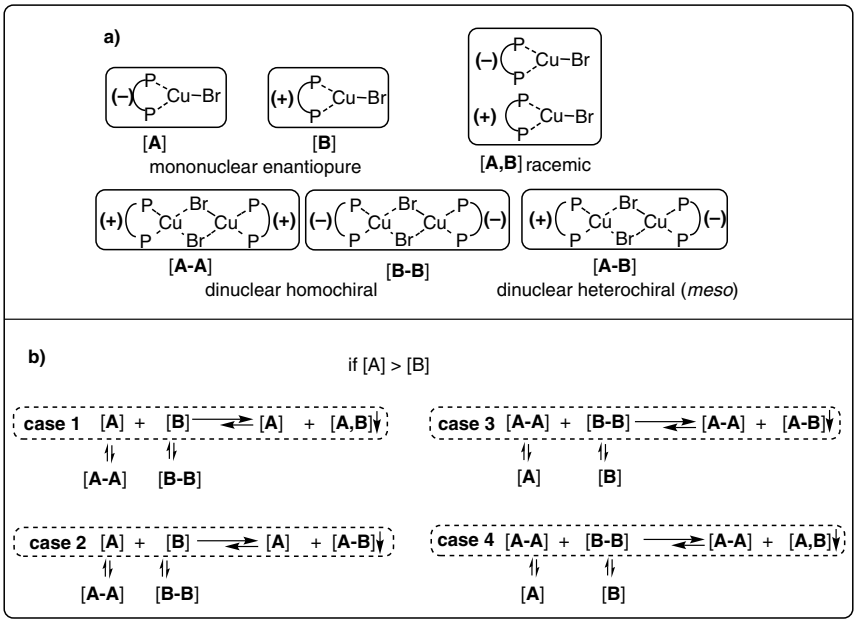
[a] Monohydrate.
[b] CH_2Cl_2 solvate.

According to the principle of 'close packing'[10] this is a sign for higher stability of the crystal. Enantiopure CuBr-rev-JosiPhos is characterised by strong intermolecular O–H···Br hydrogen bonds forming a one-dimensional chain in the crystal structure. Racemic CuBr-rev-JosiPhos has no such strong intermolecular interactions, nevertheless its density is higher than that of the single enantiomer. The exception is Cu/TaniaPhos, for which the densities of the racemic and enantiopure crystals were similar. This could be due to the co-crystallized solvent (CH_2Cl_2) in the racemic crystals.

Combined MS spectrometry, NMR spectroscopy and X-ray spectroscopy confirmed that both mononuclear and dinuclear species can be present in solution and the solid state for both the racemic and the enantiopure complexes of all ligands studied. It is a general trend that the stability of racemates is higher than that of single enantiomers;[11] however, the resulting difference in solubility is usually not sufficient to provide enantiopure supernatants through preferential crystallization of the racemate from the scalemic solution.[11]

One the other hand, the introduction of intermolecular interactions, e.g. H-bonding or ionic interactions, can amplify the solubility difference.[12]

In the present systems there is no possibility for these kinds of intermolecular interactions when free ligands are considered. Hence the formation of metal complexes acts as a surrogate for such interactions leading to the formation of mononuclear and/or dinuclear homochiral and heterochiral species (Scheme 3, a). It is reasonable to assume that this leads to the large difference in solubility of the dinuclear homo- and heterochiral species which results in an enantiopure supernatant. However, it is not necessarily the case that the precipitate is the dinuclear complex as in some cases the mononuclear complexes have been obtained as racemic and enantiopure solids. Hence, the observed solid-solution behaviour can be accounted for with large differences in solubility between (Scheme 3, b): (1) mononuclear enantiopure and racemic complexes; (2)



Scheme 3 (a) Possible copper species; (b) four scenarios to rationalise the observed precipitation phenomenon

mononuclear enantiopure and dinuclear heterochiral complexes; (3) dinuclear homochiral and heterochiral complexes; (4) dinuclear homochiral and racemic complexes. None of these cases can be excluded. What is certain is that metal complexation causes higher geometric rigidity of the complex, compared to the free ligands, which in turn enhances the differences in packing of racemic and enantiopure complexes.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(5) For details see Supporting Information.

(6) Crystal structures of enantiopure CuBr-rev-JosiPhos (CCDC 610500) and CuBr-JosiPhos (CCDC 261573) were published in ref. 4 and in: (a) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752. (b) An improved quality crystal structure was obtained for CuBr-rev-JosiPhos (CCDC 909405) during this study.

(7) CCDC 908802, CCDC 908803, CCDC 908804 and CCDC 909403 contain the supplementary crystallographic data of the corresponding complexes: *rac*-CuBr-rev-JosiPhos, *rac*-CuBr-JosiPhos, *rac*-CuBr-TaniaPhos and enantiopure CuBr-TaniaPhos, presented in this paper. For the crystal structure of enantiopure CuBr-TaniaPhos (CCDC 909403), see Supporting Information.

(8) Due to the extremely low solubility of the racemic Cu complex of rev-JosiPhos, crystals were obtained by doping one enantiomer in CH_2Cl_2 solution into poly(ethylene oxide) hydrogel followed by addition, as an antisolvent, of a solution of the opposite enantiomer in toluene. See: Choquesillo-Lazarte, D.; García-Ruiz, J. M. *J. Appl. Cryst.* **2011**, *44*, 172.

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